Alopecia universalis with unusual histopathologic features after vaccination with ChAdOx1 nCoV-19 (AZD1222)

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Key words: adverse reaction; alopecia; alopecia areata; alopecia universalis; COVID-19; SARS-CoV-2; vaccine.

INTRODUCTION

Recently, there have been rare reports detailing the onset or recurrence of alopecia areata (AA) after vaccination against COVID-19.[1-3] We report the onset of alopecia universalis (AU) in a 51-year-old woman occurring within one week of vaccination with ChAdOx1 nCoV-19 vaccine (AZD1222). A combination of typical findings and uncommon/atypical pathologic findings were identified.

Abbreviations used:

AA: alopecia areata
AU: alopecia universalis

CASE REPORT

A 51-year-old Afro-Caribbean woman with no chronic illnesses presented to the dermatology clinic with new-onset alopecia (Fig 1) involving her scalp, eyebrows/lashes, axillae, limbs, and pubic area after vaccination with ChAdOx1 nCoV-19 vaccine (AZD1222; AstraZeneca, University of Oxford). She started no new medications and received no other vaccines around this time. Before presentation, she had thick hair, denied a personal/family history of alopecia, autoimmune connective tissue or thyroid disease, and was not on medications. Intense scalp pruritus occurred 3 days after vaccination with rapid loss of scalp hair, leading to near-complete baldness within 3 weeks, except for a retained occipital patch. She received her second dose 8 weeks later and lost the remaining patch within 1 week. Pruritus and burning involving the eyebrows and eyelashes developed with accompanying loss of hair. Axillary, pubic, and limb alopecia was also noted. She sought dermatologic care. A scalp biopsy and blood work were performed (approximately 10 weeks after initial hair loss).

Transverse histologic sections revealed peribulbar lymphocytic inflammation, retained sebaceous glands, pigment in fibrous tracts, approximately 30% of hairs in catagen/telogen phase, follicular structures failing to form hair, nanogen and dystrophic hairs, empty infundibulae, profound miniaturization with small caliber hairs, and a terminal:vellus ratio of <1:1 (Fig 2, *A-F*). Although these changes were typical of AA/AU, other unusual findings were noted (Fig 3, Table I). The infiltrate was dense and mixed in nature with lymphocytes, numerous plasma cells (predominating in sections), eosinophils, and neutrophils. Inflammation involved the peribulbar, isthmic, and infundibular portions of the follicle. Intrafollicular neutrophils were present in multiple miniaturized follicles. Focal concentric perifollicular fibrosis, follicular destruction with associated multinucleated giant cells, and naked hair shafts were identified (Fig 3, *A-D*). Periodic acid—Schiff staining was negative for fungi. No perieccrine inflammation was present. Thyroid—stimulating hormone and complete blood cell count were normal. Antithyroid peroxidase and antithyroglobulin antibodies as well as enzyme-linked immunosorbent

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Funding sources: None.
IRB approval status: Not applicable.
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JAAD Case Reports 2022;25:4-8.
2352-5126

https://doi.org/10.1016/j.jdcr.2022.05.002

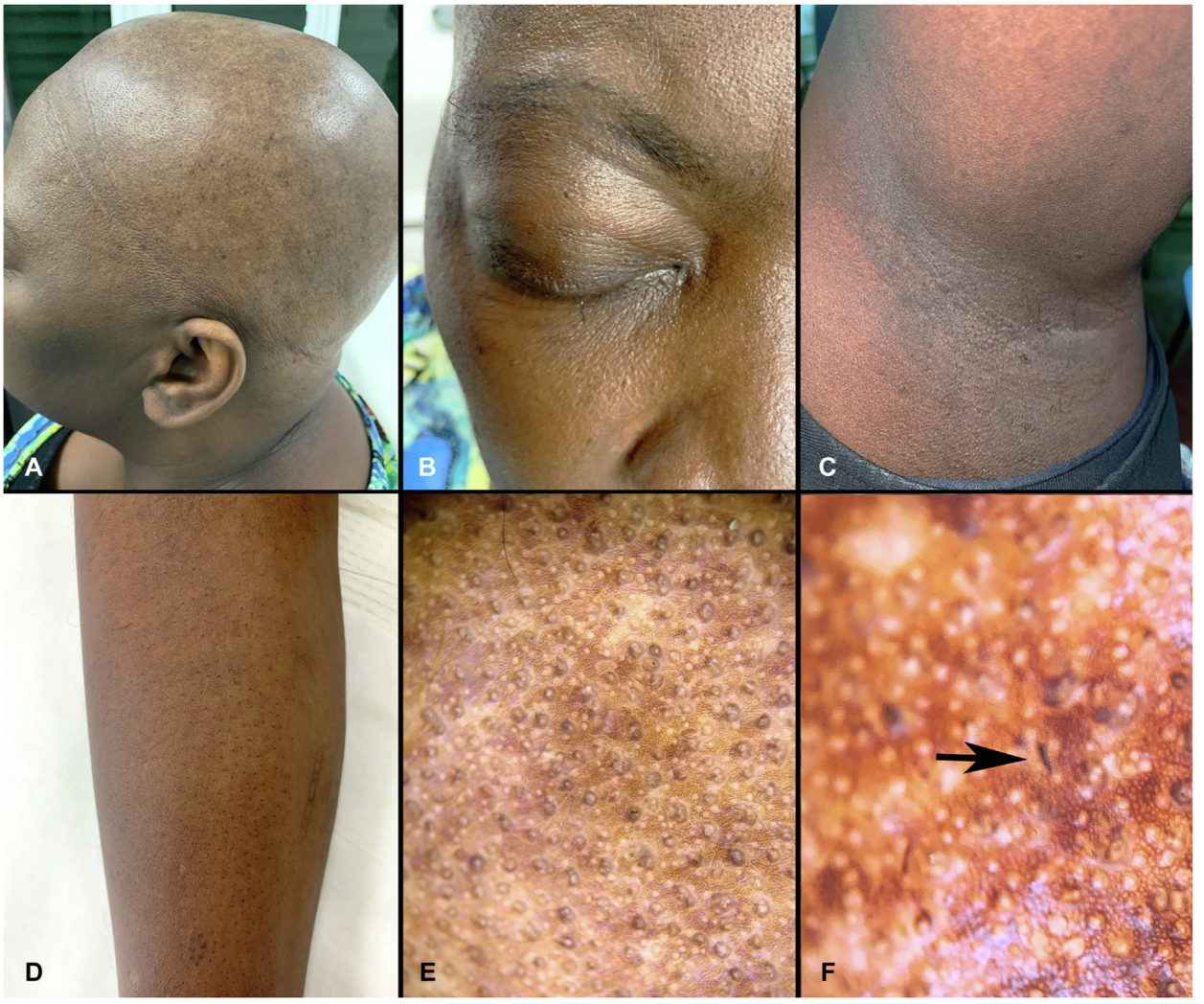

Fig 1. AU after vaccination with AZD1222. Complete loss of scalp hair with significant loss of brow, lash, axillary, and limb hair (**A-D**). Dermatoscopy demonstrated yellow dots and broken hairs (**E**), with occasional exclamation mark hairs (**F**, *arrow*)

assay analysis for antinuclear antibodies and serology for syphilis were negative. The patient was referred to us for additional input.

Examination revealed extensive scalp alopecia. No scarring, scale, pustules, or erythema was noted. Significant loss of eyebrows, eyelashes, axillary, and pubic hair were noted. Limb hair was present, but the patient reported a follicular density markedly lower than baseline (Fig 1, *A-D*). Dermatoscopy revealed broken hairs, yellow dots, and occasional exclamation mark hairs (Fig 1, *E* and *F*). Given the physical examination, dermatoscopic and some histopathologic features, a diagnosis of AU with additional unusual/uncommon microscopic findings was rendered. The patient commenced clobetasol propionate ointment under occlusion and intralesional triamcinolone acetonide 10 mg/mL (2 sessions, 4 weeks apart) while awaiting approval for oral tofacitinib. At the time of writing, she had areas of sparse white regrowth and loss of exclamation mark hairs.

DISCUSSION

Reports of hair loss following vaccination against COVID-19 are mounting.[1-4] A total of 226 cases of AA or variants thereof have been logged in association with COVID-19 vaccination in the Centers for Disease Control and Prevention Vaccine Adverse Event Reporting System database.[4] Although these are unverified and do not indicate causality or accurate classification, increasing reports in the published literature suggest potential association. A review of articles in the PubMed/MEDLINE database revealed 3 articles (13 patients).[1-3] While most cases were associated with BioNTech Pfizer and Moderna vaccines,[3] 3 cases developing after vaccination with

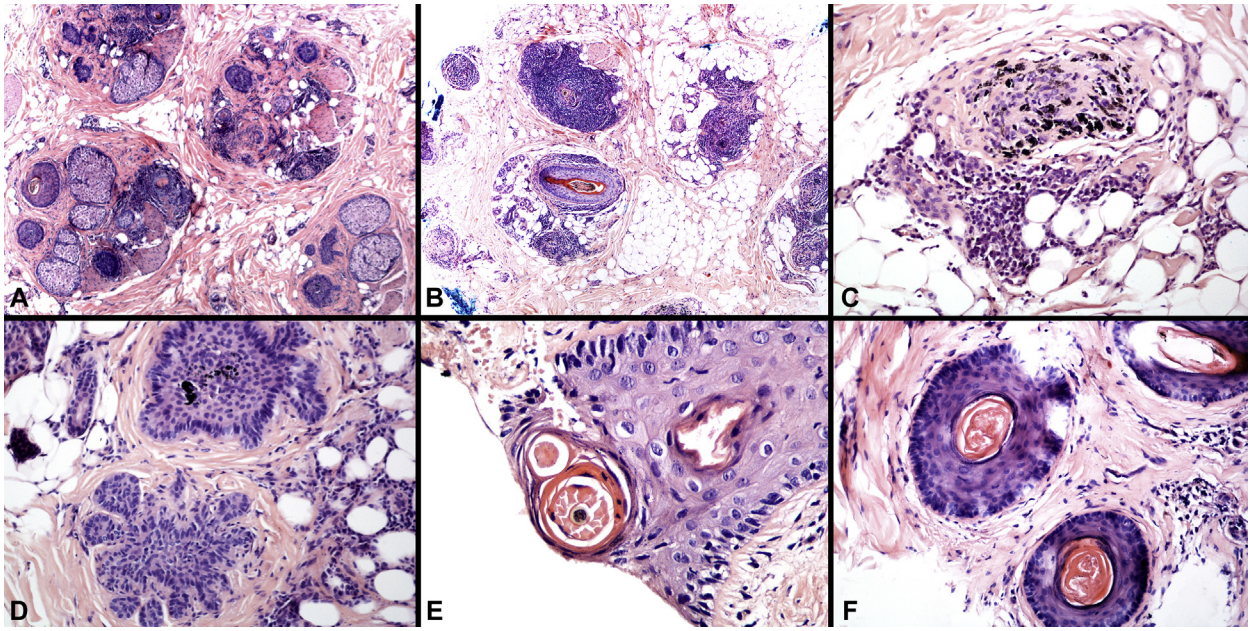

Fig 2. Typical findings of AA. Note the retained sebaceous glands (**A**), peribulbar inflammation (**B**), pigmented fibrous tracts (**C**), nonanagen hairs (**A, D**), marked miniaturization with small caliber hairs (**E**), and follicular structures failing to form hairs with empty infundibulae (**F**). (**A-F,** Hematoxylin-eosin stain; original magnification: **A,** ×40; **B,** ×40; **C,** ×200; **D,** ×200; **E,** ×400; and **F,** ×200.)

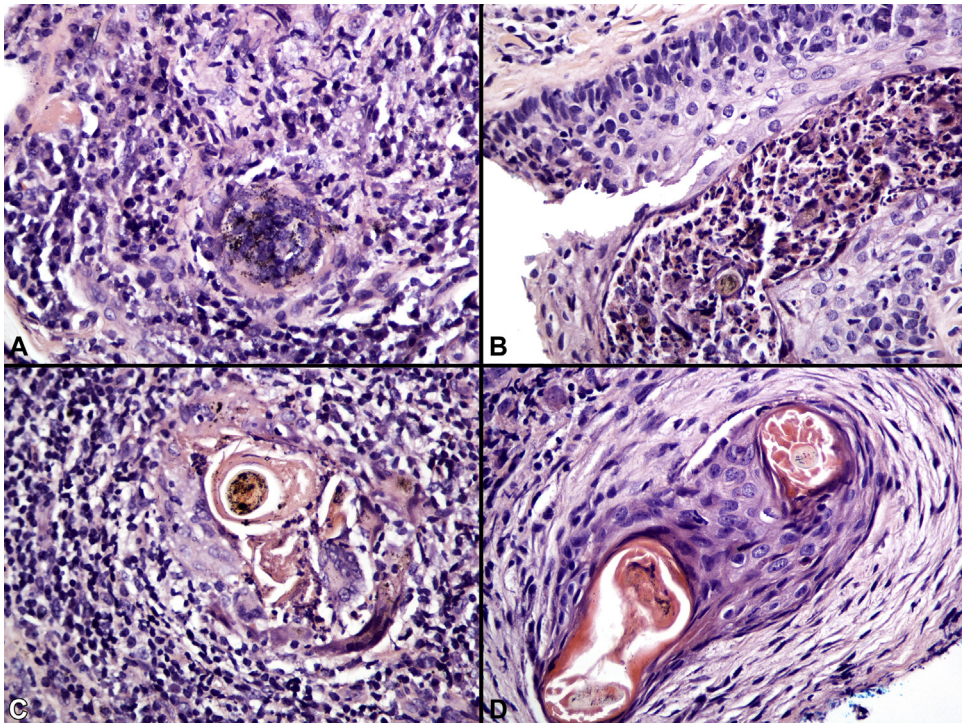

Fig 3. Atypical/uncommon findings of AA. Note the dense plasma cell-predominant peribulbar infiltrate (**A**), intrafollicular neutrophils (**B**), and follicular destruction with multinucleated giant cells with impending naked hair shaft formation (**C**). There are foci of significant perifollicular fibrosis (**D**). (**A-D,** Hematoxylin-eosin stain; original magnification: ×400.)

Table I. Comparison of typical and atypical/uncommon histopathologic features identified in a patient with alopecia universalis

Typical microscopic features of alopecia universalis	Atypical/uncommon microscopic features of alopecia universalis
Peribulbar lymphocytic inflammation ("swarm of bees")	Dense mixed inflammatory cell infiltrate at all levels of the follicle
Miniaturization with small caliber hairs	Intrafollicular neutrophils
Shift out of anagen phase	Follicular destruction
Pigment in fibrous tracts	Perifollicular fibrosis
Follicular structures failing to produce hair (nanogen hairs) and empty infundibulae	Naked hair shafts

AZD1222 have been documented.[1,2] Additionally, most patients had preexisting AA or autoimmune thyroid disease.[1-3] Patchy disease (some extensive) was most common, but 1 patient with alopecia totalis and 2 with AU have been described (Pfizer/Moderna).[3]

Our patient presented with AU beginning within the week of vaccination. Despite some retained hair, complete scalp alopecia and significant loss of body hair makes AU the best designation. She had no personal or family history of autoimmunity, thyroid disease, or alopecia. Although striking, intense pruritus prior to onset of hair loss is occasionally seen in AA and may be associated with the marked inflammation.[5] Biopsy demonstrated a combination of typical AA/AU findings in conjunction with unusual/uncommon features (Figs 2 and 3, Table I). In particular, the density and mixed nature of the infiltrate, perifollicular fibrosis, follicular destruction, and intrafollicular neutrophils are unusual/uncommon in AA/AU.[6,7] Although plasma cells and eosinophils may be seen,[6,8] the density and presence at all levels of the follicle, rather than the classic peribulbar lymphocytic "swarm of bees" is atypical. Perhaps heavier inflammation correlates with the acute nature of the disease.[6-9] Intrafollicular neutrophils are not typical of AA, and perifollicular fibrosis with follicular destruction is rare, being more common in scarring alopecias.[6-10] Collision with incidental acute folliculitis was considered and cannot be entirely excluded. However, both the patient and dermatologist denied a compatible history/examination, and intrafollicular neutrophils were observed in multiple vellus follicles in the superior isthmus-to-infundibular sections. Follicular destruction, neutrophils, and perifollicular fibrosis also raised the possibility of a folliculitis decalvans.[10] Rapid onset, absence of pustules and tufting, retained sebaceous glands, and the dermatoscopic, clinical, and other pathologic features of AA excluded this entity. None of the existing reports of COVID-19 vaccine-related AA detail histopathologic findings. Potentially, these exuberant findings are characteristic of vaccine-related AA. Additional cases with biopsy findings are necessary to determine homogeneity.

How vaccination may induce AA is unclear. AZD1222 uses a modified chimpanzee adenovirus to insert spike protein—encoding DNA into the host cell. Conversion to messenger RNA and resultant protein assembly allows production of the SARS-CoV-2 spike protein against which the host generates a T cell and antibody response.[1] Potentially, similarities between viral spike protein and hair proteins result in antibody cross-reactivity via molecular mimicry.[1] Further work elucidating the genesis of vaccine-associated autoimmunity is needed.

Although causality cannot be established, the sudden onset after vaccination, further complete loss after second exposure, lack of known autoimmune disease, and the increasing reports of this phenomenon suggest vaccination against COVID-19 may trigger/exacerbate AA.

Conclusion

Vaccines are invaluable in the fight against COVID-19. Patients with a history of AA or autoimmunity should be alerted as to the potential risk of exacerbation. This case may suggest a true association between vaccination and onset of AA/variants. Our case revealed unusual/uncommon histopathologic findings. Perhaps these features will be found to be characteristic of vaccine-related AA. Continued reporting of this phenomenon is required to further our understanding of this disease association.

Conflicts of interest

None disclosed.

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